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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,237	BLOCK, ANDREAS	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending.

Election/Restrictions

Applicant's election with traverse of group I claims 1-12 in the reply filed on 05/19/06 is acknowledged. The traversal is on the ground(s) that although patentability distinct, examination of the claims of Group I, II, and III will require a search of the recombinant viral vector of group I. Applicants argue that given the significant overlap between the subject matter of the required searches, it would not be unduly burdensome for groups I, II, and III to be examined together. This is not found persuasive because restriction requirements are set forth for reasons of patentability distinction between each independent invention so as to warrant separate search and search burden. Examiner disagrees that groups I, II and III are closely related because group I is drawn to a recombinant viral vector which contains an insert for gene expression in vitro which has distinct and different function and utilities compared to a recombinant viral vector of group II for gene expression in vivo or group III for screening agents in vitro. For example, a recombinant viral vector can be used for biological studies in vitro, wherein it could be a useful tool for basic research on the analysis of gene function or for therapeutic studies of a molecule in a subject in vivo, and therapeutic applications of an adenoviral vector, or for screening agents in vitro

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05/19/06.

Claims 1-12 are under consideration.

Claim Objections

Claim 1 is objected because it recites the term "Recombinant". The article referring to the recombinant viral vector is missing. Appropriate correction is required.

Claims 2-9 are objected because they recite the term "Vector". The article referring to the vector is missing. Appropriate correction is required.

Claim 10 is objected because it recites the term "Expression". The article referring to the expression plasmid is missing. Appropriate correction is required.

Claims 4- 9, 11, 12, are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent reference to two sets of claims. See MPEP § 608.01(n). For the sake of compact prosecution they will be interpreted to the extent they depend on claim 1 and 2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by **Fitzsimons et al**, (Gene Therapy, 8: 1675-1681, 2001).

Fitzsimons teaches a recombinant adeno-associated virus (rAAV) viral vector which contains an insert exhibiting the general structure in which, a) the $TetO_7$ is the heptamerized tetracycline operator; b) TK^+ is the minimal thymidine kinase promoter; c) tTA is a nucleic acid sequence which encodes a fusion protein from the repressor protein inducible by tetracycline and the transcriptional activation domain of the Herpes simplex virus VP16, d) CMV is the minimal cytomegalovirus promoter; e) the transgene is a nucleic acid sequence which codes for a non-viral protein luciferase; f) $intron^1$ is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp; and g) $intron^2$ is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp (p 1675, 2nd column, last paragraph and p 1676, 1st column and figure 1) as is claimed in the instant case. Thus, **Fitzsimons et al,** clearly anticipates the invention of claim 1 in the instant application.

Claims 1, 2, 5-12 are rejected under 35 U.S.C. 102(b) as being anticipated by **Nakagawa et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001).

Nakagawa teaches a recombinant adenovirus vector, which contains the transgene encoding for IL-12 controlled by the tetracycline-regulated expression system

(p 55, 2nd column, p 56 1st and 2nd column). Nakagawa teaches the utility of both two-component and one-component systems tetracycline-regulatable adenovirus vectors. Two component-systems utilize one adenovirus vector to express the transgene under the control of the TRE and a minimal promoter, and a second adenovirus vector to express the transactivator, either tTA or rTA, from a constitutive promoter (p 55, 2nd column, p 56 1st column, last paragraph). Furthermore, Nakagawa teaches one component-system, wherein both expression cassettes are incorporated into a single adenovirus vector (p 55, 1st column, last paragraph and 2nd column, 1st paragraph and reference by incorporation).

Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the transgene is a nucleic acid sequence encoding the interleukin-12 transgene as claimed in the instant application, (claim 5).

Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the insert is inserted into the E1/E3-deleted backbone of Ad5 [reference by incorporation, (Corti et al, 1999), p 55, 2nd column, 1st sentence] as claimed in the instant application, (claim 8). Thus, **Nakagawa et al**, clearly anticipates the invention of claims 1, 5, 8 in the instant application.

Claims 1, 5-12 are rejected under 35 U.S.C. 102(b) as being anticipated by **Strathdee et al,** (Gene, 229: 21-29, 1999).

Strathdee teaches the bi-directional tetracycline-regulated expression system with and without introns (figures 1 and 2 and abstract). Strathdee teaches the bi-directional autoregulated expression vectors by first removing extraneous restriction enzyme sites from the pTIG4-rTAN and –tTAN constructs (p 23 1st column last sentence-bridge- 2nd column). A portion of the expression cassette from these vectors containing the basal elements of the TK promoter, chimetic intron, transactivator coding region, and polyadenylation signal was then subcloned into the Sal/I site of the pTIG3 vector to generate pBIG3i and pBIG3r respectively (p 23, 2nd column, 1st paragraph). A selectable marker conferring resistance to hygromycin B, consisting of the bacterial hph gene expressed from the HSV thymidine kinase (TK) promoter and polyadenylation signals, was subcloned as an NruI-Sal/I fragment from the pREP4 vector backbone into the Sal/I site of the pBIG3 vectors to generate the pBIG2i and pBIG2r respectively (p 23, 2nd column, 1st paragraph). The luc+ cDNA was subcloned into the various pBIG vectors as an NheI-BamHI fragment (p 23, 2nd column, 1st paragraph). Thus, **Strathdee et al,**, clearly anticipates the invention of claims 1, 5 in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nakagawa et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001), in view of **Lode et al,** (PNAS, 95: 2475-2480, 1998).

Nakagawa teaches a recombinant adenovirus vector, which contains the transgene encoding for IL-12 controlled by the tetracycline-regulated expression system (p 55, 2nd column, p 56 1st and 2nd column). Nakagawa teaches the utility of both two-component and one-component systems tetracycline-regulatable adenovirus vectors. Two component-systems utilize one adenovirus vector to express the transgene under the control of the TRE and a minimal promoter, and a second adenovirus vector to express the transactivator, either tTA or rTA, from a constitutive promoter (p 55, 2nd column, p 56 1st column, last paragraph). Furthermore, Nakagawa teaches one component-system, wherein both expression cassettes are incorporated into a single adenovirus vector (p 55, 1st column, last paragraph and 2nd column, 1st paragraph and reference by incorporation). Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the transgene is a nucleic acid sequence encoding the interleukin-12 transgene as claimed in the instant application, (claim 5). Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the insert is inserted into the E1/E3-deleted backbone of Ad5 [reference by incorporation, (Corti et al, 1999), p 55, 2nd column, 1st sentence] as claimed in the instant application, (claim 8). Nakagawa differs from the

claimed invention by not teaching a recombinant viral vector characterized in that IL-12 is a single chain inrerleukin-12.

However, at the time the claimed invention was made, **Lode et al,** teach the efficacy of an IL-12 gene therapy approach using a genetically engineered single chain IL-12 fusion protein, constructed by linkage of the p35 and p40 genes with DNA encoding for a flexible protein linker commonly used in bioengineering of single chain antibodies (p 2478, 2nd column). **Lode** et al have also suggested the IL-12 fusion protein will simplify future vector designs for gene therapy approaches (p 2479, 2nd column). As such, Lode et al provide sufficient motivation for one of ordinary skill in the art to apply the one-component systems tetracycline-regulatable technology of **Nakagawa** for gene therapy.

Accordingly, in view of the teachings of Lode et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the the one-component systems tetracycline-regulatable technology of **Nakagawa** for gene therapy in a mouse with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification since Nakagawa teaches the temporal control of exogenous gene expression is essential for IL-12 gene therapy.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it recites the phrase "exhibiting the general structure". It is not clear as to whether the term "exhibiting" is used in reference to the general structure of the recombinant viral vector in reference to the general structure of the transgene or in reference to the order of the transactivator and the transgene or in reference to the structure and function of the insert. Further, term "general" fails to set forth how similar or different the claimed vector has to be from that iterated in the claim.

Claim 2 is vague because it recites the term "reverse". It is not clear as to what is the reverse relationship of the insert relative to what point of reference.

Claims 2-9 is vague because it recites the term "characterized". It is not clear as to what are the metes and bounds to how this is done.

Claim 3 is vague because it recites the term "inverted". It is not clear as to what is the inverted relationship relative to what point of reference.

Claim 9 is indefinite because it recites the phrase "nucleic acid sequence "represented" in SEQ ID NO: 1". In the absence of any specific range or nature to what

is represented of nuclei acid sequences "represented" besides SEQ ID: 1, the metes and bounds of the claimed invention are not clear.

Claim 10 is indefinite because it recites the phrase "nucleic acid sequence "represented" in SEQ ID NO: 4". In the absence of any specific range or nature to what is represented of nuclei acid sequences "represented" besides SEQ ID: 4, the metes and bounds of the claimed invention are not clear.

Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 11 provides for the use of a plasmid, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 11 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 12 provides for the use of a vector, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant

is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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